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## PRIORITY DOCUMENT

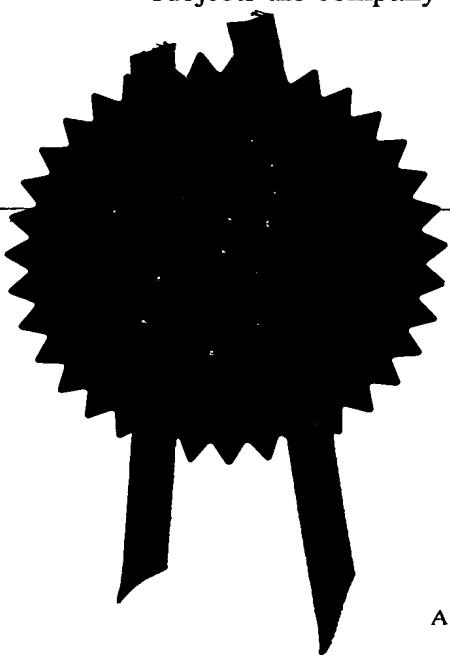
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Dated 11 April 2000



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**1/77**

07JUN99 E452422-1 D00524  
P01/7700 0.00 - 9913079.1

**Request for grant of a patent**

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

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1. Your reference **4-30972/P1**

2. Patent application number  
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**9913079.1** 04 JUN 1999

3. Full name, address and postcode of the or of each applicant  
(underline all surnames) **NOVARTIS AG  
SCHWARZWALDALLEE 215  
4058 BASEL  
SWITZERLAND**

Patent ADP number (if you know it) **7125487002**  
If the applicant is a corporate body, give the country/state of its incorporation **SWITZERLAND**

4. Title of invention **Organic compounds**

5. Name of your agent (If you have one)  
"Address for service" in the United Kingdom to which all correspondence should be sent  
(including the postcode)

**B.A. YORKE & CO.  
CHARTERED PATENT AGENTS  
COOMB HOUSE, 7 ST. JOHN'S ROAD  
ISLEWORTH  
MIDDLESEX TW7 6NH**

Patents ADP number (if you know it) **1800001**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country	Priority application number (if you know it)	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

**Yes**

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

(see note (d))

## Patents Form 1/77

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Continuation sheets of this form

Description	15
Claim(s)	2
Abstract	
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10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11.

I/We request the grant of a patent on the basis of this application

Signature

Date

B.A. Yorke & Co.

B.A. Yorke & Co.

04.06.99

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham  
0181 560 5847

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### Notes

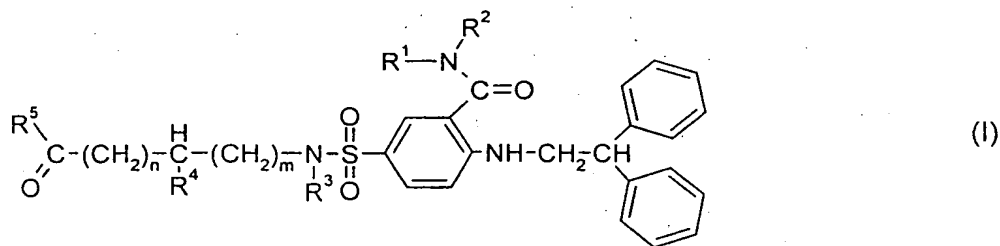
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The present invention relates to novel benzoic acid amide derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides in a first aspect, a 2-(2,2-diphenylethyl-amino)-5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid amide or -5-(aminocarbonyl-C<sub>2-4</sub>alkyleneamino-sulfonyl)-benzoic acid amide, or salt thereof.

It will be understood that the above defined compounds may bear substituents within their structure, e.g. may bear appropriate phenyl ring or alkylene moiety substituents. The amino moiety of the defined aminocarbonyl or amide groupings can be any appropriate amino grouping, e.g. cyclic or aliphatic or may bear further substituent groupings.

Preferred compounds in accordance with the invention are those of formula I



wherein

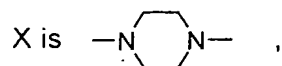
R<sup>1</sup> and R<sup>2</sup> independently are C<sub>1</sub>-C<sub>4</sub>alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring;

(a) R<sup>3</sup> and R<sup>4</sup> together are ethylene and m is 2; or

(b) R<sup>3</sup> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>5</sub>-C<sub>7</sub>cycloalkyl or phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl, R<sup>4</sup> is H and m is 1 or 2 or 3;

n is zero or 1; and

R<sup>5</sup> is -X-R<sup>6</sup> or -N(R<sup>7</sup>)R<sup>8</sup>, wherein



R<sup>6</sup> is C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>4</sub>alkenyl, C<sub>3</sub>-C<sub>4</sub>alkinyl, C<sub>1</sub>-C<sub>4</sub>(alkoxyalkyl), C<sub>1</sub>-C<sub>4</sub>(carboxyalkyl), a C<sub>5</sub>-C<sub>7</sub>heterocyclic group or phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl;

$R^7$  is amino- $C_2$ - $C_4$ alkyl or mono- or di- $(C_1$ - $C_5$ alkyl)amino- $C_2$ - $C_5$ alkyl, and

$R^8$  is H,  $C_1$ - $C_4$ alkyl or has the meanings as given for  $R^7$ ;

and salts thereof.

Alkyl groups and moieties in the compounds of formula I may be branched or straight chain.

Alkyl groups are suitably straight chain.

Heterocyclic groups as  $R^1 + R^2 + N$  may be saturated or unsaturated and may contain one or more additional heterocyclic atoms, e.g. oxygen or sulfur. Examples include piperidin-1-yl, morpholin-1-yl, 3,6-dihydro-2.H.pyridin-1-yl, thiamorpholin-1-yl and pyrrolin-1-yl.

Compounds of the invention exist in free or salt, e.g. acid addition salt form. The invention is to be understood as including both the compounds of formula I in free as well as in salt form, e.g. as trifluoroacetate or hydrochloride salt. Suitable pharmaceutically acceptable acid addition salts for pharmaceutical use in accordance with the invention include in particular the hydrochloride salt.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination:

(a<sup>1</sup>)  $R^1$  and  $R^2$  are independently methyl or ethyl.

(a<sup>2</sup>)  $R^1$  and  $R^2$  together with the N-atom to which they are attached are piperidin-1-yl, morpholin-1-yl, 3,6-dihydro-2.H.pyridin-1-yl, thiamorpholin-1-yl or pyrrolin-1-yl.

(b<sup>1</sup>)  $R^3$  and  $R^4$  together are ethylene and m is 2.

(b<sup>2</sup>)  $R^3$  is H, methyl, cyclohexyl or benzyl;  $R^4$  is H and m is 1 or 2 or 3, especially 1.

(c) n is zero or 1.

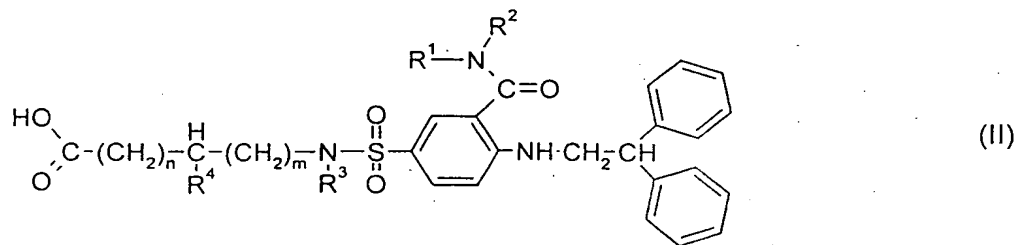
(d<sup>1</sup>)  $R^5$  is  $-X-R^6$ , wherein  $R^6$  is  $C_1$ - $C_4$ alkyl (e.g. methyl, ethyl or isopropyl), 3-propenyl, methoxyethyl, carboxymethyl, 2-pyridyl, or benzyl, and X is as defined above.

(d<sup>2</sup>)  $R^5$  is  $-N(R^7)R^8$ , wherein  $R^7$  is aminopropyl, aminobutyl, dipropylaminoethyl, dimethylaminopropyl, dimethylaminobutyl, diethylaminopropyl or dimethylaminopentyl; and  $R^8$  is H, methyl, aminopropyl, aminobutyl, dimethylaminopropyl or dimethylaminobutyl.

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In addition to the foregoing the present invention also provides a process for the production of a 2-(2,2-diphenylethylamino)-5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid

amide or -5-(aminocarbonyl-C<sub>2-4</sub>alkylene aminosulfonyl)-benzoic acid amide, for example a compound of formula I as defined above, or salt thereof, which process comprises reacting a 2-(2,2-diphenylethylamino)- 5-(4-carboxy-piperidine-1-sulfonyl)-benzoic acid amide or -5-(carboxy-C<sub>2-4</sub>alkylene aminosulfonyl)-benzoic acid amide, for example a compound of formula II



wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ , m and n have the meanings given for formula I, with an amine, e.g. of formula III



wherein  $\text{R}^5$  has the meanings given for formula I,

and recovering the obtained compound, e.g. of formula I, in free or in salt form, e.g. acid addition salt form.

The reaction may be carried out in accordance with standard procedures, for example by a first acid chloride formation step using e.g. thionyl chloride and catalytic DMF in an inert solvent, e.g.  $\text{CH}_2\text{Cl}_2$ , at ambient temperature, followed by the coupling step involving addition of the acid chloride to a mixture of the amine and e.g. TEA, at a temperature of, e.g.  $-10^\circ\text{C}$ . Aqueous workup followed by precipitation from, e.g. ethyl acetate gives the free base. The salt forms are made by standard procedures known to the skilled artisan.

In the examples the following abbreviations are used: DMF: dimethyl formamide; DMSO: dimethyl sulfoxide; EDTA: ethylenediamine-tetraacetic acid; EtOAc: ethylacetate; RT: room temperature; TBME: t-butyl methyl ether; TBTU: (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran.

**Example 1: Preparation of {2-(2,2-diphenyl-ethylamino)-5-[4-(4-isopropyl-piperazine-1-carbonyl)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone**  
(formula I:  $R^1 + R^2 + N = \text{morpholin-1-yl}$ ,  $R^3 + R^4 = \text{ethylene}$ ,  $m = 2$ ,  $n = \text{zero}$ ,  $R^5 = 4\text{-isopropyl-piperazin-1-yl}$ )

(a) A 5 liter flask is charged with {2-(2,2-diphenyl-ethylamino)-5-[4-(4-carboxy)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone (130.2 g),  $\text{CH}_2\text{Cl}_2$  (1.3 l), DMF (0.82 g) and thionyl chloride (18.1 ml, 29.51 g). The suspension is stirred at ambient temperature (the solids dissolved after ~2 h). The volatiles are removed by rotary evaporation (30°C, house vacuum) and the crude acid chloride is redissolved in  $\text{CH}_2\text{Cl}_2$  (300 ml). The solution of acid chloride is added to a mixture of isopropylpiperazine (47.60 g), TEA (98.09 g) and  $\text{CH}_2\text{Cl}_2$  (1 l) at -10°C over 1 h. The reaction is worked up by removing volatiles via rotary evaporation. The residue is suspended in EtOAc (2.0 l) and washed with water (2 x 500 ml), brine (500 ml) and dried ( $\text{Na}_2\text{SO}_4$ ). The volume is reduced by rotary evaporation (35°C, house vacuum) to ~500 ml and stirred at ambient temperature for 17 h. The suspension is filtered and dried (40°C, house vacuum) to give the title compound as free base.

(b) A 5 liter flask is charged with the above compound (121.3 g),  $\text{CH}_2\text{Cl}_2$  (1.2 l), and 37 % HCl (17.38 g). After stirring for 30 min, the volatiles are removed by rotary evaporation and the residue is triturated with IPA (1 l). The suspension is filtered and dried (40°C, house vacuum) to give the crude HCl salt of the title compound.

(c) A 2 liter flask is charged with the above crude HCl salt (133.7 g), silica gel (13.0 g) and  $\text{CH}_2\text{Cl}_2$  (1.3 l). The mixture is stirred for 15 min at ambient temperature and then filtered. This process is repeated twice more. The solvent is removed by rotary evaporation. The residue is suspended in a mixture of IPA (1.0 l) and water (100 ml) and heated to reflux. The solution is allowed to cool to ambient temperature and stir for 17 h. The resulting suspension is filtered and dried. The solid is suspended in acetone (1.0 l) and refluxed for 4.5 h. The suspension is cooled to ambient temperature and stirred for 3 days. The suspension is filtered and dried (60°C, house vacuum, 2 days) to give the title compound as HCl salt.

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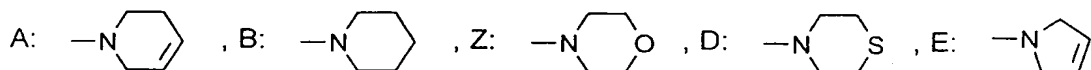
The following compounds of formula I wherein  $R^3$  and  $R^4$  together are ethylene,  $m$  is 2 and  $R^5$  is -X- $R^6$  wherein X is as defined above, are prepared analogously to Example 1:



Example	$-NR^1R^2$	n	$R^6$
2*	Z	0	$-\text{CH}_3$
3*	A	0	$-\text{CH}_3$
4	B	0	$-\text{CH}_3$
5*	Z	0	$-\text{CH}_2\text{CH}_3$
6	D	0	$-\text{CH}_3$
7*	Z	0	benzyl
8	$-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_3$	0	$-\text{CH}_3$
9*	Z	0	$-\text{CH}_2\text{CHCH}_2$
10*	Z	0	$-\text{CH}_2\text{CH}_2\text{OCH}_3$
11*	A	0	$-\text{CH}(\text{CH}_3)\text{CH}_3$
12*	Z	0	2-pyridinyl
13	E	0	$-\text{CH}_3$
14	A	1	$-\text{CH}_3$
15	Z	0	$-\text{CH}_2\text{C}(\text{O})\text{OH}$

\* as trifluoroacetate

In the above and following table A, B, Z, D and E have the following meanings:



The following compounds of formula I wherein  $R^3$  and  $R^4$  together are ethylene, m is 2 and  $R^5$  is  $-\text{N}(\text{R}^7)\text{R}^8$  are prepared analogously to Example 1: please indicate whether any of the following compounds are salts

Example	$-NR^1R^2$	n	$R^7$	$R^8$
16	A	0	$-(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	$-(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$
17	Z	0	$-(\text{CH}_2)_4\text{NH}_2$	$-(\text{CH}_2)_3\text{NH}_2$
18	Z	0	$-(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	$-(\text{CH}_2)_4\text{N}(\text{CH}_3)_2$
19	Z	0	$-(\text{CH}_2)_3\text{N}(\text{CH}_3)_2$	$-\text{CH}_3$
20	Z	0	$-(\text{CH}_2)_3\text{N}(\text{CH}_2\text{CH}_3)_2$	$-\text{H}$
21	Z	0	$-(\text{CH}_2)_2\text{N}[(\text{CH}_2\text{CH}(\text{CH}_3)_2)_2]$	$-\text{H}$
22	Z	0	$-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$-\text{H}$

The following compounds of formula I wherein R<sup>1</sup> and R<sup>2</sup> together with the N-atom to which they are attached are morpholinyl, R<sup>4</sup> is H and R<sup>5</sup> is -X-R<sup>6</sup> wherein X is as defined above, are prepared analogously to Example 1:

Example	R <sup>3</sup>	m	n	R <sup>6</sup>
23	-CH <sub>3</sub>	1	1	-CH <sub>3</sub>
24*	-CH <sub>3</sub>	1	1	-CH(CH <sub>3</sub> )CH <sub>3</sub>
25*	benzyl	1	0	-CH <sub>3</sub>
26*	cyclohexyl	1	0	-CH <sub>3</sub>
27*	-CH <sub>3</sub>	1	0	-CH(CH <sub>3</sub> )CH <sub>3</sub>
28*	benzyl	1	1	-CH(CH <sub>3</sub> )CH <sub>3</sub>
29	-H	2	1	-CH(CH <sub>3</sub> )CH <sub>3</sub>
30	-CH <sub>3</sub>	3	1	-CH <sub>3</sub>

#### CHARACTERISING DATA

Compounds 1 to 30 are found to exhibit the following HPLC retention data [min]:

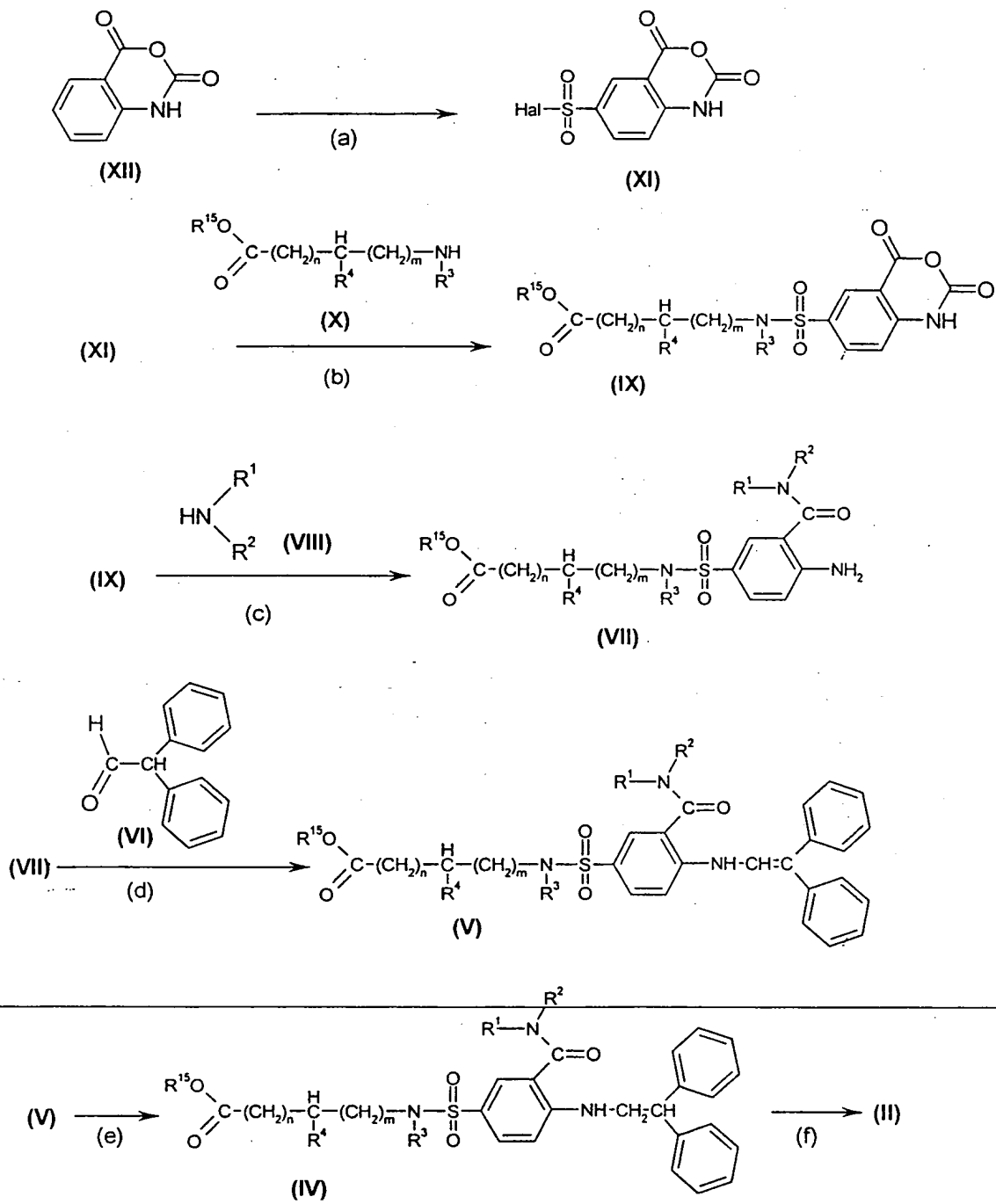
Compound	[min]	Compound	[min]	Compound	[min]
2	5.68*	11	6.37*	21	27.57***
1	5.91*	12	23.68***	22	22.9***
3	6.22*	13	5.10**	23	5.57*
4	5.43**	14	6.17****	24	5.9*
5	23.55***	15	5.28****	25	23.82***
6	5.24**	16	24.03***	26	24.95***
7	25.93***	17	4.6****	27	5.90*
8	5.09**	18	20.1***	28	6.23*
9	23.98***	19	22.6***	29	5.35*
10	23.89***	20	22.58***	30	5.75*

HPLC conditions:

- \*: Hypersil 3 micron C 18 BDS column. Gradient elution 10-100% MeCN in water (+0.1% TFA) over 10 min
- \*\*.: Kingsorb 50x4.6mm C18 column, 3micron particle size; flow rate 3ml/min; 90% water (+10mM NH<sub>4</sub>OAc 0.3% HCOOH) 10% MeCN to 100% MeCN over 10min
- \*\*\*: Nucleosil 5 micron C18 column, 25cm x 4.6mm. Gradient elution 10-100% MeCN in water (+0.1% TFA) over 40 min

\*\*\*\*: Waters Symmetry 3 micron C18 column; 5 x 0.46 cm. Gradient elution, 10% to 100% MeCN in water (+ 0.1% TFA) over 10 min

Compounds of formula II may be prepared applying known techniques, e.g. in accordance with the following reaction scheme:



wherein Hal is halogen, e.g. chlorine,  $R^{15}$  is  $C_1$ - $C_4$ alkyl, e.g. ethyl, and  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ , m and n are as defined for formula I.

Each of the above reaction steps may be carried out in accordance with conventional procedures as known in the art, e.g. as illustrated in the following examples or analogously thereto. For example in step (a) the compound of formula XII may conveniently be reacted with e.g. chlorosulfonic acid or with chlorosulfonic acid followed by thionyl chloride. In step (b) the compound of formula XI is reacted with the compound of formula X and e.g. triethylamine in the presence of a solvent like acetonitrile and acetone at  $0^\circ\text{C}$ . In step (c) the sulfonamide of formula IX is reacted with the compound of formula VIII at room temperature in the presence of a solvent like acetonitrile, acetone or ethyl acetate, ethyl acetate being preferred. Preferably an excess of the compound of formula VIII may be used, e.g. a 10 % excess. In step (d) the compound of formula VII may be reacted with an excess of the compound of formula VI, e.g. a 10 % excess, in the presence of, e.g. trifluoroacetic acid and a desiccant, e.g. trimethyl orthoacetate. The reduction of step (e) may for example be accomplished via hydrogenation over 10 % palladium on carbon in the presence of a solvent, e.g. tetrahydrofuran. The hydrolysis of the ester of formula IV [step (f)] may be accomplished in the presence of a base like NaOH, in a solvent like ethanol, methanol, acetone or tetrahydrofuran, preferably tetrahydrofuran. In some of the above steps the reactants may be warmed prior to reaction.

Starting compounds of formula III, VI, VIII, X and XII are known or may be prepared from corresponding known compounds.

**Example S1: Preparation of {2-(2,2-diphenyl-ethylamino)-5-[4-(4-carboxy)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone (formula II:  $R^1 + R^2 + N =$  morpholin-1-yl,  $R^3 + R^4 =$  ethylene,  $m = 2$ ,  $n = \text{zero}$ )**

- (a) A 2 liter flask is charged with isatoic anhydride (180.3 g) and chlorosulfonic acid (367 ml, 643.9 g). The mixture is stirred at ambient temperature for 21 h. Thionyl chloride (80.6 ml, 131.5 g) is added over 2 h and the mixture is stirred at ambient temperature for 16 h. The reaction is worked up by slowly pouring the reaction mixture over ice (4.5 kg) with stirring. The resulting suspension is filtered and the filtercake is washed with water (2 x 500 ml). The solid is dried ( $40^\circ\text{C}$ , house vacuum, 48 h) to give compound 2.
- (b) A 5 liter flask is charged with 2 (270.2 g) and acetone (2.0 l). The suspension is cooled in an ice/methanol bath and a solution of ethyl isonipecotate (165.7 g) and TEA (156.8 g) in

acetone (700 ml) is added over 1.43 h. After the addition is complete, the cooling bath is removed and the mixture is stirred for 2 h. The reaction is worked up by removing volatiles via rotary evaporation (35°C, house vacuum). The solid is triturated with 0.5 N HCl (1763 ml). The suspension is filtered and the filtercake is washed with water (1.0 l). The solid is dried (40°C, house vacuum, 3 days) to give compound 4.

(c) A 12 liter flask is charged with 4 (342.4 g) and EtOAc (3.4 l). A solution of morpholine (85.80 g) in EtOAc (340 ml) is added at ambient temperature over 1.5 h. The mixture is stirred for 30 min. The reaction is worked up by adding charcoal (35.2 g) and filtering through Celite. The solids are washed with EtOAc and the filtrate is reduced to ~2 l by rotary evaporation. Heptane (1.7 l) is added at ambient temperature over 2 h and the resulting suspension is stirred overnight. The suspension is filtered, washed with mother liquor, and dried overnight (40°C, house vacuum) to give 6.

(d) A 12 liter flask is charged with compound 6 (324.7 g) and EtOAc (4.4 l). The mixture is heated until all of the solids dissolved (~35°C). 2,2-diphenyl ethanal (164.7 g), trimethyl orthoacetate (100.8 g), and TFA (4.35 g) are added and the mixture is stirred at ambient temperature for 3 days. The reaction is worked up by removing EtOAc via rotary evaporator. The residue is triturated with TBME (3.2 l). The resulting suspension is filtered, the filtercake is washed with TBME (320 ml) and dried (40°C, house vacuum, N<sub>2</sub> purge) to give compound 8.

(e) A 2.5 liter Parr bottle is charged with compound 8 (118.8 g) and THF (1.2 l). The mixture is heated with stirring until all of the solids are dissolved (~55°C). Palladium on carbon (10 %, anhydrous, 10.47 g) is added and the mixture is shaken under a hydrogen atmosphere (50 psi) at ambient temperature for 24 h. The reaction is worked up by filtering the mixture through Celite. THF is removed by rotary evaporator. The residue is triturated with TBME (1.1 l). The resulting suspension is filtered, the filtercake is washed with TBME (110 ml) and dried (40°C, house vacuum, N<sub>2</sub> purge) to give compound 9.

(f) A 12 liter flask is charged with 9 (326.8 g), THF (3.3 l), and 1.0 N NaOH (540 ml). The biphasic solution is stirred at ambient temperature for 24 h. The reaction is worked up by removing THF via rotary evaporator. Water (1.0 l) is added to the remaining aqueous portion and 1.0 N HCl (600 ml) is added with stirring at ambient temperature over 2 h. The resulting suspension is filtered, the filtercake is washed with water (1 l) and dried (40°C, house vacuum, N<sub>2</sub> purge) to give the title compound.

Compounds of formula II, IV, V, VII and IX are new and also an embodiment of the present invention.

The following compounds of formula II wherein  $R^3$  and  $R^4$  together are ethylene and m is 2 are prepared analogously to Example S1:

Example	$-NR^1R^2$	n	Example	$-NR^1R^2$	n
II.2	Z	0	II.13	E	0
II.3	A	0	II.14	A	1
II.4	B	0	II.15	Z	0
II.5	Z	0	II.16	A	0
II.6	D	0	II.17	Z	0
II.7	Z	0	II.18	Z	0
II.8	$-N(CH_3)CH_2CH_3$	0	II.19	Z	0
II.9	Z	0	II.20	Z	0
II.10	Z	0	II.21	Z	0
II.11	A	0	II.22	Z	0
II.12	Z	0			

In the above table A, B, Z, D and E have the following meanings as defined hereinbefore.

The following compounds of formula II wherein  $R^1$  and  $R^2$  together with the N-atom to which they are attached are morpholinyl, and  $R^4$  is H are prepared analogously to Example S1:

Example	$R^3$	m	n	Example	$R^3$	m	n
II.23	$-CH_3$	1	1	II.27	$-CH_3$	1	0
II.24	$-CH_3$	1	1	II.28	benzyl	1	1
II.25	benzyl	1	0	II.29	$-H$	2	1
II.26	cyclohexyl	1	0	II.30	$-CH_3$	3	1

The compounds of the invention and their pharmaceutically acceptable acid addition salts (hereinafter: Pharmaceutical Compounds) have pharmacological activity and are useful as pharmaceuticals. In particular Pharmaceutical Compounds exhibit bradykinin antagonist activity. In particular Pharmaceutical Compounds, e.g. compounds B1 and B2, are active at the human  $B_1$  bradykinin receptor.

Bradykinin receptor interaction of the Pharmaceutical Compounds is demonstrated by their ability to displace bradykinin at human bradykinin receptor sites, e.g. as demonstrated in accordance with the following test method.

**Test I:     Bradykinin receptor binding assay**

Cloning of the human bradykinin B1 receptor cDNA: The human bradykinin B1 receptor is cloned from WI38 human foetal lung cell fibroblast cells by expression cloning in *Xenopus laevis* oocytes, which do not express bradykinin B1 receptors normally. A cDNA library is prepared in bacteriophage lambda ZAP express and grown in pools of approximately 10,000 clones per pool. Bacteriophage DNA is prepared from these pools and copy RNA is synthesised with T3 RNA polymerase and after phenol extraction and precipitation, the RNA is injected into *Xenopus* oocytes and allowed to be expressed for 3 days. The oocytes are then assayed electrophysiologically using two electrode voltage clamp, for a response in an endogenous chloride channel that can be activated by endogenous heterotrimeric GTP binding proteins of the Gq/G11 type that can couple to bradykinin receptors. A positive clone is isolated from a positive pool by several stages of splitting the pool into smaller pools and assaying, until a single clone is isolated. This cDNA is sequenced and subcloned into pcDNA3 (Clontech) and used to generate a cell-line which expresses the human bradykinin B1 receptor.

Making the HEK cells: The human bradykinin B1 receptor cDNA is subcloned into the Kpn1 and Not1 sites of pcDNA3 (HB1-pcDNA3), is grown up and transfected into human embryonic kidney fibroblast cell line, HEK 293 using the Calcium phosphate method. Cells are grown in Minimum Essential Medium with Earle's Salts (GIBCO) supplemented with 2 mM L-glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin, 1 % nonessential amino acids and 10 % myoclone foetal calf serum (GIBCO) in a humidified atmosphere with 5 % CO<sub>2</sub> at 37°C.

The 293Hek cells are split 1:2 the day prior to transfection. One 175 cm<sup>2</sup> flask with approximately 50 % confluent cells is transfected with approximately 30 µg/ml HB1-pcDNA3 DNA using the calcium phosphate precipitate method of transfection. The flask of transfected cells is split 1:3 on day 2 post transfection to prevent overgrowth. The following day the cells are split 1:5 and selection in 700 µg/ml G418 begins. The selective medium is changed every 3-4 days. When distinct G418 resistant colonies of transfected cells are seen, approximately 4 weeks after transfection, the cells are cloned by limiting dilution and assayed for binding of [<sup>3</sup>H]desArg<sup>10</sup>-kallidin. The clone with the highest binding is chosen for further use. Care is

taken not to allow the cells to overgrow and to maintain G418 in the growth medium.

These HEK 293 cells expressing the human bradykinin B<sub>1</sub> receptor are used to prepare membranes. Cells are homogenised in 50 mM Tris-HCl, 1 mM EDTA pH 7.4 at 10,000 rpm for 30 sec in a Polytron homogeniser. All subsequent operations are carried out at 4°C. The resultant suspension is centrifuged for 30 min at 28,000 x g. The pellet is washed a further two times by resuspension in Tris-HCl (50 mM, pH 7.4) and recentrifugation. The final pellet is resuspended in Tris-HCl (50 mM, pH 7.4), containing 5 % glycerol and frozen rapidly on dry ice in 500 µl aliquots and stored at -80°C.

For use in the binding assay, membranes are thawed, homogenised, and diluted with physiological binding buffer (10 mM HEPES, HBSS {137 mM NaCl, 5.4 mM KCl, 1.3 mM CaCl<sub>2</sub>, 0.4 mM KH<sub>2</sub>PO<sub>4</sub>, 0.3 mM NaHPO<sub>4</sub>, 0.5 mM MgCl<sub>2</sub>, 0.4 mM MgSO<sub>4</sub>, 5.6 mM glucose, pH 7.4} containing 1 mM 1-10 phenanthroline and 0.14 g/l bacitracin. Binding assays are performed in 1.2 ml polypropylene assay tubes (incorporated into a deep well block of 96 or individual Micronics tubes) containing a final volume of 0.5 ml. The assay composition is 425 µl membrane suspension (approximately 20 µg protein per tube) in physiological binding buffer, 50 µl [<sup>3</sup>H]desArg<sup>10</sup>-kallidin (specific activity 95 Ci/mMol; 6.0 ± 0.5 nM), 25 µl of either DMSO, or unlabelled desArg<sup>10</sup> kallidin (20 µM) or different concentrations of test compounds made up in DMSO. Specific binding to the bradykinin B<sub>1</sub> receptor is defined as the difference between that found in total bound tubes and that found in non-specific binding tubes. The reaction is initiated with the addition of membranes and incubated at 4°C for 60 min. The reaction is terminated by rapid filtration of the assay mixture through Canberra Packard Unifilter-96 GF/B filterplates (which have been pre-soaked in 0.6% polyethyleneimine for 2 to 3 h at RT). The filters are washed 4 times with 1 ml aliquots of ice cold wash buffer. Microscintillant-40 liquid scintillant is added to the filters and radioactivity bound is determined in a Canberra Packard Topcount scintillation counter. Binding parameters are derived from non-linear iterative curve fitting of three or four data sets simultaneously, using a logistic model in Microcal<sup>TM</sup> Origin.

K<sub>i</sub> values are 0.063 µM for the peptide antagonist desArg<sup>10</sup>HOE [(D-Arg-[Hyp<sup>3</sup>, Thi<sup>5</sup>, D-Tic<sup>7</sup>, Oic<sup>8</sup>]desArg<sup>9</sup> bradykinin) = (D-Arginine-[hydroxyproline<sup>3</sup>, thienyamine<sup>5</sup>, D-tetrahydroxyquinoline-3-carboxylic acid<sup>7</sup>, octahydroindole-2-carboxylic acid<sup>8</sup>]desArginine<sup>9</sup> bradykinin)] and in the range of 0.5 nM to 2 µM for pharmaceutical compounds.

Pharmaceutical Compounds are accordingly useful as bradykinin B<sub>1</sub> receptor antagonists, e.g. in the treatment of diseases and conditions in which B<sub>1</sub> receptor activation plays a role or is



implicated. Such conditions include in particular pain, in particular chronic pain, especially inflammatory, e.g. chronic inflammatory pain, inflammatory diseases for example inflammatory airways disease, e.g. COPD, or in asthma, rhinitis, inflammatory bowel disease, cystitis, e.g. interstitial cystitis, pancreatitis, uveitis, inflammatory skin disorders and rheumatoid arthritis.

Pharmaceutical Compounds are thus useful as bradykinin BK<sub>1</sub> receptor antagonists, e.g. for the treatment of pain of various genesis or aetiology and as anti-inflammatory and/or anti-oedemic agents for the treatment of inflammatory reactions, diseases or conditions, as well as for the treatment of allergic responses mediated by bradykinin. Having regard to their analgesic/anti-inflammatory profile they are useful for the treatment of inflammatory pain, for the treatment of hyperalgesia and, in particular, for the treatment of severe chronic pain. They are, for example, useful for the treatment of pain, inflammation and/or oedema consequential to trauma, e.g. associated with burns, sprains, fracture or the like, subsequent to surgical intervention, e.g. as post-operative analgesics, as well as for the treatment of inflammatory pain of diverse genesis, e.g. for the treatment of osteo and rheumatoid arthritis and rheumatic disease, teno-synovitis and gout. They are further suitable as analgesics for the treatment of pain associated with, e.g., angina, menstruation or cancer. As anti-inflammatory/anti-oedema agents, they are further useful, e.g., for the treatment of inflammatory skin disorders, for example psoriasis and eczema.

As bradykinin BK<sub>1</sub> receptor antagonists Pharmaceutical Compounds are also useful as smooth muscle relaxants, e.g. for the treatment of spasm of the gastro-intestinal tract or uterus, e.g. in the therapy of Crohn's disease, ulcerative colitis or pancreatitis.

Pharmaceutical Compounds are in particular useful as agents for the therapy of airways hyperreactivity and for the treatment of inflammatory events associated with airways disease, in particular asthma. In addition, Pharmaceutical Compounds may, for example, be used for the control, restriction or reversal of airways hyperreactivity in asthma.

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Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic and, especially, extrinsic asthma. Thus, Pharmaceutical Compounds are useful for the treatment of allergic asthma, whether atopic (i.e. IgE-mediated) or non-atopic, as well as, for example, exercise induced

asthma, occupational asthma, asthma induced following bacterial infection, other non-allergic asthmas and "wheezy-infant syndrome".

Efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack and by reduced requirement for other, symptomatic therapy, for example anti-inflammatory (e.g. corticosteroid) or bronchodilator (e.g.  $\beta_2$  adrenergic) therapy.

Inflammatory or obstructive airways diseases to which the present invention is applicable further include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and, in particular, byssinosis.

Further inflammatory or obstructive airways diseases and conditions for which Pharmaceutical Compounds may be used include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), and bronchitis. Pharmaceutical Compounds may also be used for the treatment of allergic and vasomotor rhinitis (add "whatever is in Dorland's" (Gordon's input)).

In addition to the foregoing Pharmaceutical Compounds are also indicated for use in the therapy of septic shock, e.g. as anti-hypovolaemic and/or anti-hypotensive agents, in the treatment of inflammatory bowel disease cerebral oedema, headache, migraine and inflammatory skin disease such as eczema and psoriasis, and inflammatory disorders of the gut, e.g. irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystitis, e.g. interstitial cystitis, nephritis, uveitis. Pharmaceutical compounds are also indicated for use in the treatment of Alzheimers disease and as anti-proliferative agents for the treatment of cancer.

For the above indications the appropriate dosage of Pharmaceutical Compounds will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated as well as the relative potency of the particular Pharmaceutical Compound employed. However, in general, satisfactory results in animals are indicated to be obtained at daily dosages of from about 0.01 to about 20.0 mg/kg p.o. In humans, an indicated daily dosage is in the range of from about 7.0 to about 1400 mg/day p.o.,

conveniently administered once or in divided doses up to 4 x per day or in sustained release form. Oral dosage forms accordingly suitably comprise from about 1.75 or 2.0 to about 700 or 1400 mg Pharmaceutical Compound admixed with an appropriate pharmaceutically acceptable diluent or carrier therefor.

Pharmaceutical Compounds may alternatively be administered e.g. topically in the form of a cream, gel or the like for example for the treatment of conditions of the skin as hereinbefore described or by inhalation, e.g. in dry powder form, for example for the treatment of asthma.

Pharmaceutical Compounds are also useful as research chemicals.

In accordance with the foregoing the present invention also provides:

- (1) A pharmaceutical compound for use as a bradykinin BK<sub>1</sub> receptor antagonist, for example for use in any of the particular indications hereinbefore set forth;
- (2) A pharmaceutical composition comprising a pharmaceutical compound as under (1) as active ingredient together with a pharmaceutically acceptable diluent or carrier therefor;
- (3) A method for the treatment of any of particular indication hereinbefore set forth in a subject in need thereof which comprises administering an effective amount of a pharmaceutical compound as under (1); and
- (4) A process for the preparation of a compound as under (1).

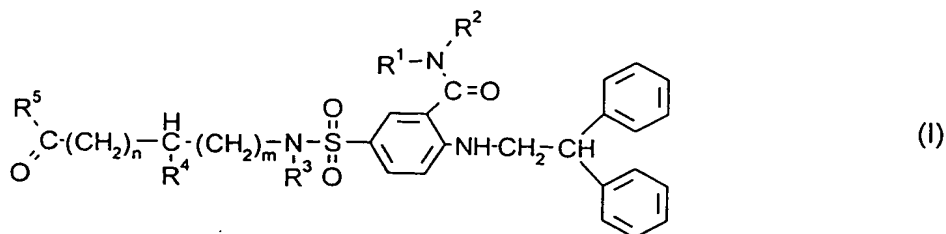
The preferred Pharmaceutical Compounds for use in accordance with the invention are those of Examples 1 and 2.

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# Claims

1. A 2-(2,2-diphenylethylamino)- 5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid amide or -5-(aminocarbonyl-C<sub>2-4</sub>alkylene aminosulfonyl)-benzoic acid amide, or salt thereof.

2. A compound according to claim 1 of formula I



wherein

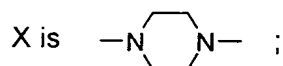
R<sup>1</sup> and R<sup>2</sup> independently are C<sub>1</sub>-C<sub>4</sub>alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring;

(a) R<sup>3</sup> and R<sup>4</sup> together are ethylene and m is 2; or

(b) R<sup>3</sup> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>5</sub>-C<sub>7</sub>cycloalkyl or phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl, R<sup>4</sup> is H and m is 1 or 2 or 3;

n is zero or 1; and

R<sup>5</sup> is -X-R<sup>6</sup> or -N(R<sup>7</sup>)R<sup>8</sup> wherein



R<sup>6</sup> is C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>3</sub>-C<sub>4</sub>alkenyl, C<sub>3</sub>-C<sub>4</sub>alkinyl, C<sub>1</sub>-C<sub>4</sub>(alkoxyalkyl), C<sub>1</sub>-C<sub>4</sub>(carboxyalkyl), a C<sub>5</sub>-C<sub>7</sub>heterocyclic group or phenyl-C<sub>1</sub>-C<sub>4</sub>alkyl;

R<sup>7</sup> is amino-C<sub>2</sub>-C<sub>4</sub>alkyl or mono- or di-(C<sub>1</sub>-C<sub>5</sub>alkyl)amino-C<sub>2</sub>-C<sub>5</sub>alkyl, and

R<sup>8</sup> is H, C<sub>1</sub>-C<sub>4</sub>alkyl or has the meanings as given for R<sup>7</sup>;

and salts thereof.

3. Pharmaceutical composition comprising, or use of, a 2-(2,2-diphenylethylamino)- 5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid amide or -5-(aminocarbonyl-C<sub>2-4</sub>alkylene aminosulfonyl)-benzoic acid amide, or pharmaceutically acceptable salt according to claim 1 substantially as hereinbefore described.

4. 2-(2,2-diphenylethylamino)- 5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid amide or 5-(aminocarbonyl-C<sub>2-4</sub>alkylene aminosulfonyl)-benzoic acid amide, or pharmaceutically acceptable salt according to claim 1 for any use substantially as hereinbefore described.

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